REMARKS

Claims 1-21, 43-46 and 48-65 are pending. No new matter has been added. The Applicant reserves the right to prosecute any withdrawn or cancelled subject matter in one or more continuation or divisional applications.

We were very pleased to note that the Examiner indicated that claims 19-21 are allowable if rewritten in independent form. However, the Examiner continues to reject the remaining claims as anticipated under 35 U.S.C. §102(e) or rendered obvious under 35 U.S.C. §103(a).

Rejection under 35 U.S.C. §102(e)

The Examiner has rejected claims 1-8, 13, 17-18, 43, 48, 60 and 62 under 35 USC §102(e) as anticipated by Hawley et al (US 2006/0242722A1). The Examiner states that the priority date of Hawley predates the priority date of the instant application and that Hawley teaches the production of piglets using cell clones lacking wild type α-1,3-galactosyltransferase (αGT) wherein the expression of α(1,3)galactosyltransferase activity was negative, as well as organs and cells from such animals.

As the Examiner is aware, §102(e) dictates that a person shall be entitled to an invention unless the invention was described in a published application or patent by another filed in the United States 'before the invention' by the applicant. The Applicant respectfully notes that both conception and reduction to practice of the present invention was completed prior to Hawley's provisional filing date. To support this, a declaration by Carole Phelps, the sole inventor in the present case, is attached, supporting that the pigs described in the present case were conceived of and were indeed born prior to Hawley's priority date. Given that actual reduction to practice of the presently claimed animals predated Hawley's priority filing date, the Applicant respectfully request that this rejection under 102 (e) be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner has also again rejected claims 1-18, 44-46, 49-59, 61, and 63-65 under 35 U.S.C §103(a) over Lai et al. (*Science*, 295: 1089-1092, February 2002) in view of Straham, et al. (*Frontiers in Bioscience*, 1, e34-41, 1996). The Examiner concedes that Lai produced only heterozygous pigs, but asserts that Straham provides the motivation to breed homozygous knock out pigs because it indicates that the Gal-α-1,3-Gal (α-Gal) epitope was the major target for human anti-pig antibodies. The Examiner further states that because αGT null mice had been produced, it would not have been anticipated that this genetic modification would be lethal in the null animals.

As noted previously, the Applicant does not dispute that the art recognized a need for αGT-negative swine, but instead asserts that there was simply no expectation in the art that such animals would be viable. The Examiner has asserted that any such skepticism was overcome when it was shown αGT-negative *mice* were viable. However, as previously discussed, at the time of filing there were well recognized differences in α-Gal epitope expression between mice and pigs, based on which one of ordinary skill in the art would have lacked any expectation that results obtained in mice could be applied to pigs. Furthermore, the art was filled with statements supporting that a person of ordinary skill in the art would *not* believe that any αGal-negative pigs would be viable. The Applicant supported these assertions with references including:

- Tanemura and Galili (2000) *Transplantation Proceedings*. 32:843), which showed that pig organs express *between 10 and 500 times* the α-Gal levels of mice organs and that these raise the concern that "pigs may not be able to develop in the absence of α-gal epitopes";
- Galili, U. ((2001) *Biochimie* 83:557-563), which notes that the abundant expression of α-Gal in pigs as compared to *all other animals* throws doubt onto whether a homozygous αGT-negative animal would survive;
- Ayares et al. ((2001) *Graft* 4:80-85), which notes "[since] Gal epitope expression in pig organs is up to 500-fold higher than in mouse organs, there is the possibility that αGT activity is more crucial to the pig";

- Sharma et al. ((2003) *Transplantation* 75:430-436), which notes "it is possible that GT(-/-) pigs may not be viable because the GT gene is essential for embryonic development";
- Porter & Dallman ((1997) *Transplantation* 64:1227-1235), which notes "[a]lthough [αGT-negative mice] develop and remain fairly normal, the possibility exists that deletion of this enzyme could have more severe consequences in other animals;" and
- Denning et al. ((2001) *Nature Biotech* 19:559-562), which showed actual lack of success in producing viable αGT sheep when attempts were made to produce such animals.

The Examiner has not challenged any of this evidence. Indeed, the Examiner appears to accept that there were art recognized differences between αGal expression in pigs and mice, and that the reference presented "raise the concern that the abundantly expressed a-gal epitope may have some biological roles in pig development." The Examiner, however, goes on to note that "Lai teaches [αGal] null mice have already been produced, and it is not anticipated that this genetic modification will be lethal in null animals" and apparently uses this to state that the combined teachings of Lai and Strahan "suggest the survival" of homozygous pigs.

The Applicant notes that the Examiner has provided no evidence that supports that a person of ordinary skill in the art would ignore the well recognized differences between pigs and mice and the multiple references that noted that pigs, in contrast to mice, were expected to lack viability. The Applicant has provided more than five separate references, predating the present invention, that articulate the expected lack of viability of the αGal-negative pigs. The Applicant has even provided evidence that, when such a mutation was attempted in another ungulate, it was *not* successful. The debate on this matter supports that a person of ordinary skill in the art at the relevant time would have lacked any reasonable expectation that such animals would be viable.

The Applicant has provided substantial evidence to show that one of ordinary skill would not have expected *any* combination of the references cited by the Examiner to produce viable pigs lacking functional expression of αGT, as presently claimed. Only with the Applicant's present invention did the hope for viable pigs lacking functional α-Gal become a reality. The Applicant respectfully requests withdrawal of this rejection.

The Applicant believes no additional fees are required with this response. Should the Examiner determine otherwise, the Commissioner is authorized to charge any underpayment of fees to Deposit Account No. 11-0980.

Respectfully submitted,

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